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## THE DETERMINANTS OF SPREAD OF EBOLA VIRUS DISEASE — AN EVIDENCE FROM THE PAST OUTBREAK EXPERIENCES

**Abstract:** The paper summarizes available evidence regarding the determinants of spread of Ebola virus disease, including health care and community related risk factors. It was observed that the level of uncertainty for the estimations is relatively high which may hinder to make some predictions for the future evolution of EVD outbreak. The natural history of EVD has shown that the disease may pose a problem to developed countries and may present a threat to individuals. Although observed modes of transmission mainly include direct contact and contaminated staff, high case fatality ratio and frequent contacts among individuals in developed countries are among determinants which may lead to the development of the EVD outbreak.

**Key words:** Ebola virus infection, spread, risk factor, determinants, chain of infection, source, transmission, replication number.

### INTRODUCTION

The Ebola virus infection (EVI) has appeared as one of the emergency public health concern in 2014. The problem become to life with the development of Ebola virus disease (EVD) outbreak in Africa recognized on March 10, 2014 in Guéckédou, Guinea [1]. The outbreak developed rapidly through unprotected borders to Liberia, Sierra Leone, and next, by the airline connection to Nigeria. In the period March 2014 till Aug. 1, 2014 the EVD was diagnosed and attempted to fight down in African region only. Starting on Aug. 2, 2014 the first EV case was recognized in the US [2]. This event raised an emergency alert to health authorities. The current outbreak has been caused by the Zaire Ebola virus strain [3], which was observed to have very high case-fatality ratio (reaching 89% [4]), therefore, a real threat to public health has been evolved. Several papers have been published and different possible scenarios for the EV spread have been proposed and discussed. Considering the fact, that the current EVD outbreak is still out of control (Nov., 2014), the aim for this manuscript was to summarize available knowledge about the chain of EV infection, to describe

determinants of the EVD spread, and to discuss the risk of EVD outbreak in developed countries.

## THE SPREAD OF THE EV DISEASE

There are some components required for the development for every infectious disease. They are called as the chain of infection, which is defined as “a process that begins when an agent leaves its reservoir or host through a portal of exit, and is conveyed by some mode of transmission, then enters through an appropriate portal of entry to infect a susceptible host” [5]. The Centers for Disease Control and Prevention presents conditions which must be met in order for a microbe or infectious disease to be spread from person to person as causative agent, reservoir (source), portal of exit, mode of transmission, portal of entry and susceptible host [6]. Therefore, for the prevention and control measures every element of the chain of infection should be carefully investigated and consequently, any possible preventive measures should be applied for every component of the process.

## THE RESERVOIR (SOURCE)

The EVD is thought to be a zoonosis. Several investigations have been made to identify the reservoir of EV. Primates were considered as rather unlikely to be the reservoir as it was observed that they were susceptible to the development of the disease while infected [7]. Investigations have shown some evidence that fruit bats may be the reservoir of the Zaire EV. This was concluded after a discovery of three tree-roosting species: *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata* having natural infection identified by the viral RNA and antibodies [8]. Some other evidence pointing on fruit bats comes from 2007 and 2008. Investigation performed in Kitaka Cave in western Uganda following a limited outbreak of Marburg hemorrhagic fever identified Egyptian fruit bats, *Rousettus aegyptiacus*, as a possible reservoir for the Marburg virus (MV) — a virus from the “Ebola” group. This research provided additional knowledge, as researchers obtained positive isolates from *R.aegyptiacus* caught in August 2007 and in May 2008 implying colonies of *R.aegyptiacus* could harbor MV for longer periods of time [9]. Other documented animal sources of epidemic pointed on chimpanzees, gorillas, monkeys, porcupines and forest antelopes. Detailed observations, however, have shown that these species should be considered as hosts rather instead of reservoir [10].

## THE TRANSMISSION PROCESS

One of the first known outbreak of EV in the Democratic Republic of the Congo in 1976 was mainly attributed to the reuse of contaminated needles showing that blood was one of the important or even the major mode of transmission that time. The EV outbreak in 1979 appeared as a consequence of hospital dissemination of EV involving 5 families and the subsequent spread of the infection among family members. On site evaluation revealed several risky conditions at local hospital included no running water in the patient care areas, limited supply of masks, caps and gowns, a lack of routinely practice nursing barriers, infrequent sterilization of hospital instruments. It was observed that relatives of hospitalized patients frequently provided routine nursing practices as handling emesis, excreta and soiled clothing. The analysis of this outbreak revealed that close intimate contact with ill person associated with nursing care led to 5-fold increase in the risk of infection. It also suggested that the EV is not easily transmitted via the airborne route. Persons kept with EVD cases in poorly ventilated huts did not develop the disease unless they had a direct physical contact [11]. Next epidemic observed in Kikwit, a city of around 200.000 inhabitants in the Democratic Republic of the Congo in 1995, enabled to identify and quantify exposures that were predictive of risk for secondary transmission of the EV. Analyses revealed that the major risk factor was a direct physical contact with an ill family member both, at home at less severe stages of the disease and in hospital at more severe stages. Other risky behaviors identified were: a) reported contact with body fluids of an ill person, b) being an adult family member, or c) sharing a bed during late illness, and in late stage of the disease d) sharing a meal, and e) having a conversation. Moreover, touching of cadaver was also identified as a risk factor. The study of the 1995 outbreak did not find an increase in the risk associated with any exposure (considering conversation, sharing a bed and touching) during incubation period as well as exposures like sharing a meal, conversation and sharing a bed during an early illness [12].

As there were much more EVD outbreaks, some other risks have been identified and/or verified [13]. An investigation of the 2000/2001 Uganda outbreak additionally enabled to assess the length after the onset of the disease when the virus was observed by the culture or the RT-PCR in some specimens. The shorter time (of 6 days) was observed for skin during the acute disease, and the longer for semen in convalescents (being as long as 40 days). Another positive samples were saliva, breast milk, stool, tears, and nasal blood [14]. The summary of the identified risk factors and the associated increase in the risk is presented in Table 1.

Table 1

Risk factors for being infected by Ebola virus.

	Risk increase (*)	Reference
Exposure to contaminated medical instrument	7.4 (95% CI: 1.6–33.2) <sup>MV</sup>	[23]
Intimate contact associated with nursing care	5.1 (95% CI: 1.31–15.48)	[11]
Care for patient: — cared only during patient's early stage — cared until the patient's death at hospital — cared until the patient's death at home	p for trend <0.001 6.00 (95% CI: 1.33–27.10) 8.57 (95% CI: 1.95–37.66) 13.33 (95% CI: 3.20–55.59)	[13]
Direct physical contact with an ill family member (in home or at hospital)	29.5% of family members of this type contact became infected, but no-one with no such contact increase in the risk — undefined	[12]
Contact with body fluids of an ill	3.6 (95% CI: 1.9–6.8) 5.30 (95% CI: 2.14–13.14)	[12] [13]
Being an adult family member	4.6 (95% CI: 2.0–10.3) 6.7 (95% CI: 2.4–18.4)	[12] [24]
Sharing hospital bed	3.4 (95% CI: 1.8–6.2)	[12]
Sleeping on the same mat	2.78 (95% CI: 1.15–6.70)	[13]
Exposures during late illness: — sharing a meal — conversation — sharing a bed	2.2 (95% CI: 1.2–4.0) 3.9 (95% CI: 1.2–12.2) 2.2 (95% CI: 1.2–4.2)	[12]
Cadaver toughing	2.1 (95% CI: 1.1–4.2)	[12]
Ritual hand washing during funeral	2.25 (95% CI: 1.08–4.72)	[13]
Communal meal during funeral	2.84 (95% CI: 1.35–5.98)	[13]

CI — confidence interval; (\*) — majority of these estimates are the results of univariable models, therefore they may account from other co-existing risk factors; MV — estimate for Marburg virus type

## THE SUSCEPTIBLE HOST

The review of the currently available evidence does not reveal any known natural resistance for EV infection. Therefore, vaccination seems to be the only reasonable solution for preventive measures in this area. Although there is no licensed

vaccine available to prevent EVD, a considerable progress has been observed in recent years. There are some vaccine platforms, which are currently under investigation including: virus-like particles (VLPs), Venezuelan equine encephalitis virus replicons (VEEV RP), replication competent recombinant human parainfluenza virus 3 (rHPIV3), replication incompetent adenovirus vectors, and recombinant vesicular stomatitis virus (rVSV) [15–17]. Only two of the aforementioned vaccines presented promising results. The study of Recombinant Chimpanzee Adenovirus Serotype 3 Vectored Ebola Vaccine (cAd3 Ebola vaccine) has found that in non-human primates, which were given a lethal dose of EV, the vaccine protected, with a single treatment, of 100% of 16 laboratory animals. The second promising vaccine is recombinant VSVΔG-ZEBOV — in a pre-exposure pre-clinical study in 20 non-human primates this vaccine has shown the efficacy of 100%, and post-exposure vaccination has led to 50% survival rate [15]. Future results of human clinical trials will reveal the efficacy for these vaccines, however, these results have shown that some primary prevention strategies may be available soon [18].

## NATURAL HISTORY OF EV INFECTION

The clinical course of the EV infection is presented in the other article in this issue, therefore, this paragraph is to present some data what is known about the dynamics of the spread of the disease across susceptible individuals. It is rather unlikely that EV has its own reservoir in North America or in European countries, therefore the risk of the spread of the EV infection in these regions is determined only by the ‘imported’ cases. In African region, however, where the EV disease causes outbreaks, some epidemiological data suggests the presence of some trigger factors causing spillover events of EV from a natural reservoir or from an intermediate host into men. Although these introductions were frequently unrecognized or were not reported correctly, there are some observations suggesting that these events occurred with some pattern associated with climatologic variables as quick shift from dry to wet conditions [19] or lower temperature and higher absolute humidity [20]. The risk of the transmission of the EV depends on the risky behaviors (see before and the Table 1) and the stage of the disease in the natural development of the EVD (Fig. 1). The determinants of the dynamic of transmission include: mode of transmission (see before), population density, frequency of contacts among individuals at the population level, infectivity of the pathogen (EV), and the susceptibility of the host (see before). Preventive measures implemented at the population level may significantly change the dynamic of transmission. If there is no preventive measures, the average number of secondary cases in a completely susceptible population caused by a typical infected individual throughout the entire course of infection is called the basic

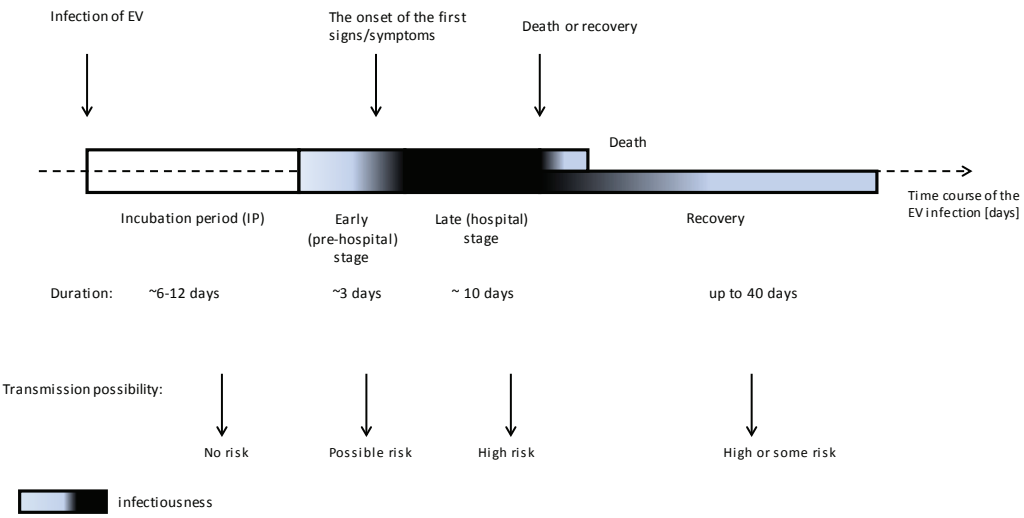


Fig. 1. The natural course of the EV infection and the associated risk of the EV transmission to susceptible individuals.

Table 2

Estimated basic reproductive numbers ( $R_0$ ) for EVD outbreaks.

Outbreak (year)	Basic reproductive number ( $R_0$ )		Transmission rate (per week)	Reference
1976	Congo	4.71 for community component (including funerals): 1.34	nd	[25]
1995	Congo	1.83	2.31	[26]
		3.07	nd	[27]
		2.7 for community component: 0.5	9.04 0.59	[4]
2000/2001	Uganda	1.34	0.38	[26]
		2.7 for community component: 2.6	4.01 3.53	[4]
		2.13	nd	[27]
2014	Guinea	1.51	0.27	[28]
	Sierra Leone	2.53	0.45	[28]
	Liberia	1.59	0.28	[28]

nd — no data

reproduction number ( $R_0$ ). The epidemic may develop only if  $R_0 > 1$ , otherwise, the spread of the disease is self-limiting. The basic reproductive number calculated for the EVD has been estimated to range from 1.34 to 4.71 (Table 2). The basic reproduction number for the EV varied, depending on the mode of transmission which is the main determinant of the spread in the particular population. The highest  $R_0$  was observed for the 1976 outbreak caused mainly by the contaminated needles. At the population level, habitual contacts accounted for  $R_0$  of 0.5 in 1995 Congo outbreak to 2.6 in 2000/2001 Uganda outbreak. Although the past EVD outbreaks were frequently self-limiting, the emergence of the EV infection spread in high density populations leads to the conclusion that the only solution is the implementation of extensive prevention and control measures.

#### THE POSSIBILITY OF THE EBOLA VIRUS OUTBREAK IN DEVELOPED COUNTRIES

The health care in developed countries is much better organized and financed than in experiencing EVD outbreak African countries. Therefore, the possibility to prevent and control the development of EVD outbreak is incomparably higher in our region. Until Nov. 30, 2014 there are at least 22 known imported cases of EVD: 10 in the US [21], 3 in Spain, 3 in Germany, 2 in France and 1 in Britain, Norway, Switzerland and Italy [2]. All these countries developed very quickly every possible preventive measures. Additionally, intensive surveillance strategies have been implemented, and consequently, until now, there is no known spread of the EVD in these countries. As some of the 'imported' cases, before they developed clinical symptoms severe enough to raise awareness and to be hospitalized, had a contact with their family, co-workers and other people in the surrounding environment, there was a possibility to infect some other individuals. As it was rather unlikely, there is still open for discussion a possibility of the transmission of the EV from the infected person before the development of clinical symptoms. The investigation of 1995 EV outbreak showed that 4 family members, who had been exposed to infected person during pre-hospital phase only, developed the disease. As it was not recognized finally, when these 4 family members might have contact, there is no credibility, nowadays, for the lack of transmission in the early stages of the disease.

There are publications available, which show the scenarios of the development of the EVD outbreak in developed countries. Chowell and Nishiura in their review published the 'probability of no major outbreak' in a population of 100.000 associated with different determinants. Considering the size of the spillover event (the number of initial cases) they have calculated that this probability is higher than 60% for 1 initial case, but drops dramatically to approximately 20% for 3, and to 10% for 5 initial cases. Another critical component was the period between

the onset of EVD symptoms and the proper diagnosis of the disease. If this time takes 3 days instead of 1 the probability of 'no major outbreak' decreases by about 2.5-times. The crucial component mentioned by authors was the time from the spillover event to the implementation of control interventions. If the time equals 5 days there is almost no risk for the development of the EVD outbreak, however, if the delay prolongs to 33 days the probability of 'no major outbreak' goes below 25% [22].

## SUMMARY

Available evidence regarding the risk quantification for different exposures to EV provides evidence with high level of uncertainty, which may hinder to make some predictions for the future evolution of EVD outbreak. The natural history of EVD has shown that the disease may pose a problem to developed countries and may present a threat to individuals. Although observed modes of transmission include direct contact and contaminated staff, high case fatality ratio and frequent contacts among individuals in developed countries are among determinants which may lead to the development of the EVD outbreak. Therefore, the available knowledge about the spread of the EV support any increase in the effort to limit current EVD outbreak.

## DISCLOSURES

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